Sokoloff, Louis 2005

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Claudia Wassmann: This is Claudia Wassmann and today's date is Thursday, March 3rd, 2005. I am conducting an interview with Dr. Louis Sokoloff.

CW: Dr. Sokoloff, let me first thank you for doing this interview with us. I feel very privileged and honored. And I would like to address three points today, and that is the history of the development of the deoxyglucose method, the evolution of the uses of PET here at the NIH, and the surprises that this research yielded for you when you look back at your own career. So maybe you could start with telling us about how you got here, what brought you here.

Louis Sokoloff: Well it's a long story. I had gotten interested in basic science back in college, and did some undergraduate research in basic science with cell blast physiologist Heilbrunn. But the war was on, going on, World War II, and Heilbrunn instead of accepting me for a PhD under him, he recommended that I go to medical school because his graduate students were all being drafted into the army, but if I went to medical school I would be deferred until I finished because the army needed doctors. So I went to medical school, and after medical school I had to intern. At that time in the state of Pennsylvania, they required a rotating internship, which meant that you had to spend time on every one of a number of services, surgery, medicine, gynecology, obstetrics, laboratory medicine, neurology, psychiatry.

So I had some neurology and psychiatry during my rotating internship, which was normally a year but had been compressed to nine months because of the war, it went on an accelerated program. And I had neurology and psychology during my rotations. Then the war ended, so they wanted to go back to the one-year internship schedule, and to get back on a July 1st- June 30th period schedule, my class got an extra six months provided we stayed on one service, and they put me on psychiatry. When I finished my internship, I had to join, get into the army as an army medical officer. And because I had so much experience already in neurology and psychiatry, the surgeon general of the Army United States ordained me a neuropsychiatrist. And I was assigned to be Chief of Neuropsychiatry, at that time, Camp Lee Station Hospital, and I did neuropsychiatry for two years.

CW: Were there questions you were particularly interesting in?

LS: I was interested in -- from my internship I had gotten kind of interested in this strange behavior of the mind. Of course the psychoanalysts said it had nothing to do with brain, it had to do with the mind. It could have been anywhere; it could have been in the big toe. Because they weren't dealing with physical things, they were dealing with abstract concept of mind. But I was interested in what happens to a -- I believed it has something to do with the brain. What happens to the brain to make a person schizophrenic? So I was interested, I did the best I could, but we were dominated then by psychoanalytic thinking. I became enough interested in it so that when I had to decide what I was going to do when I got out of the Army, the Army period was only for two years. And I had to make a choice between coming back and going in and completing my psychiatric training so I could pass the Boards. However I was also interested in basic science, and I believed that whatever was going on in these mental diseases had something to do with the brain and I wanted to do some basic science studies of the brain. It so happened that about a year before I was due to get out of the Army, my old teacher from the University of Pennsylvania Medical School, Seymour Kety, had published a number of papers on the new method that allowed one to measure the rate of blood flow and the rate of oxygen consumption and glucose utilization in the brain of human beings. And, very importantly, while they were conscious unanesthetized, because what's the point in studying an anesthetized brain, it wouldn't -- no one's normal.

So when I came out of the Army I went back to Philadelphia where I originally came from and I stayed for a few weeks at my mother's home, and hadn't decided yet what I was going to do. Then once I decided after a few weeks, I went up to see Dr. Kety at the University of Pennsylvania and asked if I could come and work with him and learn his method and take part in his research because I was interested in using it to study the brain of the human beings with or without mental disease. And he took me as a post-doctoral fellow, and we used this method; this was the nitrous oxide method for measuring cerebral blood flow and metabolism in man. We used this method, and in conditions where -- pathological conditions where brain function was obviously abnormal, we could find changes in energy metabolism.

CW: So how did you measure that, how did you see your results at that time?

LS: You actually had a method using nitrous oxide that you would measure in the arterial blood and the cerebral venous blood. Seymour Kety had developed a formula from which you could calculate blood flow. And since we were measuring arterial concentration and the venous, cerebral venous concentrations, you have what's called an arterial venous difference. If you multiply cerebral blood flow by arterial venous difference you can measure the rate at which the brain is either using or producing certain substances. Well, in conditions like coma, this was diabetic coma, uremic coma, hepatic coma, unconsciousness, we could measure these changes in oxygen consumption of the brain -- energy use of the brain went down. But then when we went to look at physiological conditions, we found that -- like for example, in natural sleep, we couldn't find a change in oxygen consumption. And performing a mental arithmetic, we couldn't find a change. In schizophrenics it was normal oxygen consumption, and so it was a puzzle.

There were people at that time who, in the field, who were saying, "Well that's not surprising because mental functions don't take any energy," or, "such infinitesimal amount of energy that you can't detect it." We didn't believe it; we believed the problem was that the nitrous oxide method measured the average blood flow or oxygen consumption of glucose utilization of the whole brain, as a whole. And the abnormal functions that we -- or the normal functions that we wanted to look at were in specific parts of the brain, which got lost when you measure the average of the whole brain. So we needed a method that would measure these functions in individual parts of the brain as specific anatomically units of the brain as possible. But there was no such method, certainly not for man, and not even for animals. There were ways of recording single parts of the brain with an electrical recording techniques with electrodes, but what you got depends on where you put your electrode. If you didn't know where to look, it wouldn't help. So we became interested in having methods for local blood flow or metabolism.

Seymour Kety had left the University of Pennsylvania and had come here to the NIMH. He was the first scientific director of the NIMH when it had been newly established, and a couple of years later he asked me to come and join them. And he had worked out the theory of a method that could be used to measure blood flow in individual parts of the brain. This involved the use of radioactive isotopes, and what we needed was a radioactive gas because we knew gases cross the blood brain barrier without any restrictions, so you needed that to measure blood flow. The gas was labeled with radioactive iodine, I-131, trifluoroiodomethane, and a group of us led by Seymour Kety, a group that included here at NIMH, Walter Freygang, William Landau, Bud Rowland and myself, worked for a couple, few years, and developed this method. And it allowed us to -- now the theory of the method required that we deal with a homogenous tissue. The nitrous oxide method could average the whole brain, white matter, gray matter, didn't matter. But this method, to be valid, you had to have pure gray matter, pure white matter, and so on. And the reason we thought by cutting out pieces of brain, we would get, be able to pick out parts [?]. But that wasn't very practical because we could never separate the gray and the white by just dissecting it.

But then the idea occurred of using autoradiography. You would freeze the brain at the end of the experiment, then cut it into -- the frozen brain into slices, and we would put x-ray film against the frozen brain slices along with calibrated radioactive standards and we'd expose the film, and the radioactivity in the brain tissue would be reflected in the images in the film, and with the standards we could measure the darkness, the optical density of the standards and get a calibration curve relating concentration to optical -- to how dark it was. So we had a quantitative way of measuring the local concentrations of the tracer, and from the theory of the method, you can relate that to the concentration of the tracer in the arterial blood and you can calculate local blood flow.

CW: So when was that?

LS: Well, that was -- I think the first report of that method was in 1955, and it was reported in the Transactions of the Americans Neurological Association, but that was just normal and anesthetized cats. Of course we had to kill the cat at the end of the experiment to get the brain out. Now then, once we had this method we decided now maybe we could use it to look at functional activity, would that change blood flow, and could you use the changes in blood flow to identify which parts of the brain were involved in this function? And so, we continued these experiments in cats, and we looked at the effect of visual stimulation and we studied cats with their eyes closed, we had to sort of sew the lids together. And by the way these were conscious animals, because anesthesia changes brain function, so we didn't want anesthesia.

So we studied the animals conscious with their eyes shut or with their eyes sewn open with a light flash, flashing in their eyes, and we could see all the parts of the visual system in the cat's brain. It showed increases in blood flow, which you can see on the autoradiograms. This was published in 19 -- it was a meeting that we presented in 1960 and it came out in a book in the '61 proceedings of this meeting as the first demonstration ever of imaging functional activity of the brain on the base of a physiological function, in this case blood flow.

It was around this time, 19, around 1956 to 1959 that Niels Lassen from Copenhagen came as a post-doctoral fellow in our lab. And he didn't help in this particular project but he knew what was going on, and when he went back to Copenhagen he and David Ingbar from Lund, Sweden, adapted the same principles but instead of using autoradiography, of course in humans you can't do that, you put scintillation counters over the brain and they could measure changes in blood flow in the cortex of human beings using, instead of using trifluoroiodomethane, radioactive xenon. And they could get changes in -- and they didn't image the brain, but what they did is they had, I think they had eventually end up with 256 detectors over the brain. And then they would guess which parts of the brain these detectors were looking at, and they superimpose it on a picture of the brain, and so it was a pseudo-imaging thing.

CW: At that time the radio chemicals, were they already produced at the NIH, or where did you get them?

LS: No, no. Well, NIH never produced the radioisotopes. We had to buy the radioisotopes. In the case of the original trifluoroiodomethane, we could not get any company that was interested in making it. So we would buy from Oak Ridge radioactive I-131 iodine, and we synthesized the trifluoroiodomethane gas ourselves. I-131 iodine has an eight day half-life, so when we synthesize it, it would decay whether we used it or not, and it took about a week to purify it. So once we made -- so we would spend one week making the gas, purifying it, and another week using it, then we'd have to go back and make it. So it wasn't a very practical method. But we used it; nobody else in the world ever used it.

Later on, much later on, we adapted for using it with something that was available, radioactive carbon-14 labeled iodoantipyrine, which is not a gas but it diffused across the blood brain barrier, so that's now the standard for use in animals, but that's another story; let's go back to the original.

Now, I had become more interested in the metabolism of the brain, than in the blood flow. I think that was probably stimulated by the -- switch in interest, it was stimulated by Bill Landau, who was one of the people who worked earlier in this blood flow method. He was a neurophysiologist normally, but he helped us with the blood flow studies because we didn't have any fellows of our own at the time. But he was very sarcastic about blood flow measurements. He said, "Well, what are you interested in blood flow for? That's only plumbing. What's that got to do with the function of the brain?" "The only use for the blood flow is that it be there. That's the only time it's important. It becomes important only when it's not there. Once it's there, it means nothing, how are you going to tell what's going inside the house by looking at the sewage coming in and out of the house?" And you know, there was something to be said about that.

So I became interested in biochemistry, energy metabolism, and so I thought, "Blood flow, even if it does have something to do with functional activity, is going to be diffuse. Functional activity involves individual cells. There is not a single cell anywhere in the brain that has its own private blood flow. So if you stimulate one cell, the blood flow will increase to the whole region, but metabolism would be -- should be associated with individual cells, and the question was we weren't sure whether functional activity affected energy metabolism, but we felt that it would be better to have a method that measured local metabolism rather than local blood flow.

The idea of doing that was to use a method, a radioactive precursor of energy metabolism that we could use for the autoradiographic method to get localization, but that was a problem. Oxygen has a radioisotope O-15, oxygen is a substrate for energy metabolism. To measure oxygen consumption you need radioactive oxygen, well it has a two-minute half-life. Well, we couldn't work with a two-minute half-life with autoradiography. Same thing, so we couldn't use oxygen consumption. Now it so happens that in the brain almost all of the oxygen consumption is used for glucose oxidation. And in fact glucose is almost the only substrate other than oxygen that's used for the brain's energy metabolism; only trace amounts of others are used. So we figured, "Well, maybe we can use radioactive glucose. That's labeled, you can label that with C-14 -- carbon 14, and that was commercially available, and measure -- well the problem there was it didn't work, because, actually we never even did the experiments because we -- I had learned from my interest in physiology, I was in the physiology department at the University of Pennsylvania. I had learned to do modeling and mathematics and so on, so I made a model of what would happen with glucose, and found that in order to measure the rate of glucose metabolism, one has to measure the rate of the accumulation of a product. But glucose gets oxidized in carbon dioxide and water, which leaves the brain very quickly as its being made.

So when I tried to work out this model, I found that it would be impossible, you know, to get accurate values because we wouldn't know how much glucose had been converted to the product, because the product was being lost. By the time we got to do the autoradiography it'd be gone, or much of it lost. So I dropped it, and in fact I have first -- I have notes back in 1955, I know I really starting to do that, so I just dropped it.

In 1957, I was writing a chapter for the "Handbook of Physiology" on the metabolism, the central nervous system in vivo. And I was writing the section on why glucose is not only the preferred substrate for energy metabolism by the brain, but is an essential substrate. If you don't have glucose, the brain won't work. So there'd been a lot of experiments in the literature, a lot of reports in the literature that if you lower the blood glucose level, like with insulin, you lose consciousness. And if you inject glucose, you bring back the consciousness. But I was looking for something other than insulin hypoglycemia so that I could avoid the problem -- maybe this was having some other action other than the effect of glucose. Something that -- some other evidence that it was really low glucose that was responsible, not the insulin effect, some other effect.

So I was talking to Donald Tower who was the Chief of the Laboratory of Neurochemistry, the Neurology Institute, and his lab was right across the hall from mine, about this. And he said, "You know, why don't you go up and see Bernard Landau in the Heart Institute," this was in old Building 10, "He's doing some interesting experiments with a compound which is not glucose, but is an analog of glucose, which he's giving it to patients with cancer. He's injecting very large doses, very large doses, and they go into a coma that looks exactly like hypoglycemic coma, the kind of coma you get when you give too much insulin, but it's not due to any insulin, and in fact the blood glucose is high, it goes up with it, but they go into coma and it looks like it's interfering with the brain's glucose metabolism." Well, nothing had been published yet, but it sounded very interesting, and in fact in that chapter I have a reference to unpublished data, personal communication about this. That this might be evidence that the brain really needs glucose, that if you block the brain's glucose metabolism, the brain won't work.

CW: So that was new at that time, too.

LS: Yeah. But I became interested in why did the deoxyglucose produce coma? In fact, it produced it in the [unintelligible] higher -- increased blood glucose level. And I follow this up, the literature, I didn't do anything myself about it, just followed the literature. And then around, I think the paper was published in '57, but I didn't became aware of it until '59, paper by Wick, W-I-C-K and Drury, that showed why it produced coma. It wasn't because it competed directly with glucose, because there's a lot of glucose in the blood and there's a lot of glucose in the brain, so that you would need much more deoxyglucose than they gave to produce coma if it were interfering with the transport of glucose across the blood brain barrier or with the phosphorylation of glucose by exokinase, so that couldn't have been the explanation.

What they found was the reason it produced coma was the oxyglucose was being converted to deoxyglucose-6-phosphate, just like glucose was being converted to glucose-6-phosphate, to glucose-6-phosphate. But the oxyglucose-6-phosphate accumulated, it couldn't go any further because it didn't have an oxygen -- on the second carbon, it couldn't deconvert to fructose-6-phosphate like glucose did. So glucose would go through and go on to pyruvate and lactate and get oxidized. But the oxyglucose with the deoxygluse-6-phosphate, it stopped, and the oxyglucose-6-phosphate got bigger -- higher concentrations, increased to a point where it exceeded the concentration of glucose-6-phosphate. It blocked the conversion of glucose-6-phosphate to fructose-6-phosphate. In other words, it blocked glycolysis. And I remember when I saw that I said, "That might be a way to get around the problem with glucose. If I could use deoxyglucose instead of glucose, then I would have a product that accumulates and I could determine how much deoxyglucose was metabolized, and it must be related to how much glucose was, thus they would compete." Someday I should be working on that. I filed it away. That was '59.

I was busy at that time working with -- I had stopped working on blood flow and metabolism of the brain, and I started working on the effects of thyroid hormones on protein synthesis. And the reason I had switched to that was because while I was still at the University of Pennsylvania, we were looking for a condition that would increase oxygen consumption of the brain. And we couldn't find any, so we thought of using hyperthyroidism because in hyperthyroidism the whole body oxygen consumption goes up. And so, we had patients that -- where the average oxygen consumption of the whole body was increased, I think, an average of 70%. And we measured their cerebral oxygen consumption with the nitrous oxide method, Kety and Schmidt, and normal oxygen consumption. So I became interested. Why doesn't the brain have an increased oxygen consumption like the rest of the body in hyperthyroidism? Well from looking at the literature and thinking about it and everything else, I became -- I got the idea that in the mature brain, once its matured, the rate of protein synthesis and turnover in the brain goes down very low, while carbohydrate metabolism is high, maybe it's because of that. Maybe the reason why thyroid hormones stimulate oxygen consumption is because they stimulate something having to do with protein synthesis, which that second [unintelligible] more oxygen.

So the question is, do thyroid hormones affect protein synthesis? So later on when I came to NIH, I ran into Dr. Seymor Kaufman who was a very good biochemist, and he was interested in the same problem. So we collaborated and I learned most about biochemistry from him on this project and in fact found that thyroid hormones do stimulate protein synthesis.

CW: So you were -- it looks like at the very beginning, the whole research has been impacted a lot by World War II and the research project that we're going on during World War II.

LS: That's right.

CW: And then interfered this or molecular biology.

LS: Well it's not molecular -- of course we were working with molecules, but the word molecular biology started when they started working with DNA.

CW: Yeah, wasn't that 1953, the DNA that they discovered the structure of DNA?

LS: Yeah, right. But at that time we weren't talking about DNA.

CW: Oh, okay.

LS: So, I was busy with that project because we had found -- in fact we published that in 1959, Kaufman and I in *Science,* that thyroid over-stimulated protein synthesis, and we were interested now in the reason why, how -- what was the mechanism? So I was busy with that, so the dioxyglucose idea was set aside, someday I'll get around to working on it, but right now I'm busy with this. And this went on and on.

In 1964, Ribich came to the lab as a post-doctoral fellow who was interested in studying cerebral blood flow and metabolism, and at that time Seymour Kety was working on schizophrenia and I was working on thyroids, but we thought, "Well, he came specifically for cerebral blood flow, so let's start a project to get on cerebral blood flow, but what would be a good project for him to work on?" Well, the old trifluoroiodomethane for local blood flow, the autoradiographic method, was impractical because you had to synthesize the gas; it's difficult to work with the gas. What we need is a non-gaseous diffusible substance that we could use to measure blood flow. It uses a tracer to measure local blood flow with the autoradiography method, and preferably something that was labeled with carbon-14 that has a five thousand year half-life; you don't have to synthesize it all the time, don't have to keep buying it. And also, it should, on the autoradiographs, give us much better, sharper resolution, because it's a weaker energy beta radiation.

So he, with the assistance a technician, we had Jane Jearly, adapted the trifluoroiodomethane, the iodo-trifluoroiodomethane method for use with carbon-14 antipyrine, and they adapted for doing the autoradiography with the carbon-14 labeled tracer. Well at that time Kety and Ribich and I would meet once a week at a meeting, maybe a lunch meeting or so on, and I remember saying, "Gee," this was down around 1966 [laughs]. You know? "Now that we have a method for carbon-14 labeled autoradiography, maybe now it's time to do something about the oxyglucose, we could label that with carbon-14, and use carbon-14 autoradiography." Yep, yep. Yes, we ought to get around to that.

In '66, Ribich went back to the University of Pennsylvania and he called me one day and he said, "You know I'm applying for a grant and you had talked about this deoxyglucose thing, are you still interested?" And, "Yes." He said, "Well, would you be interested in collaborating, and I'll put something in my grant application for this about developing the method." So I said, "Yeah, but you know, at the moment my laboratory was doing all these biochemical studies, we wouldn't be able to do these animal studies. They would have to be done in your lab." "Yeah, sure. That's okay."

So I guess it was around 1967 the experiments started in Ribich's lab, on seeing whether deoxyglucose and glucose would be taken up by brain in a proportionate way. And so the experiments were done with brain slices to show that they would -- they increase in perfect linear relationship to each other in up tight by the brain, which showed -- well it looks like it's being metabolized in proportion to the glucose metabolism. So it looked good. So we developed a model, you know, a model of these -- making a diagram of all the steps and end up applying mathematical analysis to it, and ended up with a model was based simply on the blood flow equation that Seymour Kety had developed, plus an extra term for trapping it as a metabolite. And there was nothing wrong with the model, nothing wrong with the equation, except it required measuring blood flow, and with a blood flow tracer and the deoxyglucose at the same time, and it involved having parameters that were impossible to determine. So it was theoretically fine, but practically impossible. So it was sort of sitting there.

In 1968, I decided it was time, it was my last chance to take -- at that time the NIMH had a sabbatical leave program, and it was going to be my last chance to -- I've been there since 1953 and if I'm going to take advantage of the sabbatical this will be my last chance. I took a sabbatical, and I went to Paris to the Laboratory of Jean Roche, which was probably the world's leading laboratory for thyroid biochemistry. Their interest is mostly in the synthesis of thyroid hormones, the thyroid gland. And I figured if I don't want to work on the actions of the thyroid hormones, I'm doing that in my own lab. If I go somewhere else on sabbatical, I would want to go somewhere where I work in something new that I could learn.

So I went there, and they had a project going on -- related to the synthesis of thyroid hormones. The way thyroid hormones are synthesized is the thyroid gland makes a protein which is a thyronine -- thyroid globulin, sorry, thyroid globulin. It's a big long protein, which has a lot of tyrosine residues in it. And in the thyroid gland, there's a peroxidase reaction, thyroid gland peroxidase that catalyzes the reaction that takes iodine and iodinates these tyrosine residues, and from that forms triiodothyronine, tetraiodothyronine, which is thyroxine, and iodinated thyroid hormones. And they had been studying -- they found that they could use a model system. Instead of using thyroid gland tissue, they could serum albumin, which the protein has some tyrosine in it, and the radioactive iodine. And if they added some peroxide or a hot peroxide generating system that would make hydrogen peroxide thick, they were able to iodinate the protein, and they were using this model system. But the kinetic behavior, this system is very strange. It didn't follow straight Michealiean -- Michaelis-Menton kinetics. So I got interested, because from my physiology background I had done a lot of modeling, mathematics, and kinetics was something that I was interested in. In fact, in a way, blood flow is kinetics; something flows.

So I got into that project and in the course of that I had to learn a lot about enzyme kinetics. I spent the whole year doing enzyme kinetics really, and then it occurred to me maybe we should change our approach to deoxyglucose method, and deal with it not as a blood flow trapping system, but as a pure enzyme kinetics problem, and deal with it from that. And now I had become very good with the mathematics for studying kinetics. So when I came back at the end of the year, my project on thyroid, effects of thyroid hormones that had been going on in my lab while I was gone had stopped. Nothing happened in a year [laughs]. So I had to decide should I resurrect that project or maybe it's a good time to drop it, and now start working on the deoxyglucose method. So that's what I decided to do. I'm switching over, I'll forget about the thyroid effects of protein synthesis for a while anyway, and get involved with this.

And so, developed the model and we -- our first experiment in a rat where we injected the radioactive deoxyglucose and did the autoradiography, which gave beautiful PET images, was in February 1971. In 1974, we reported it for the first time in rats, for working rats. We reported it at the American Society for Neurochemistry [unintelligible]. And then it was all working, and we published in 1970 --

CW: So you were interested in thyroid hormones for a long time in between --

LS: Oh yeah.

CW: You really let that sleep [?] from the --

LS: Yeah, but there's a continuation. It wasn't -- I think there are scientists who read a paper in the literature, they said, "Let's go work on it." And that's not the way I was trained and not -- ours was a sequence, a logical sequence of following. Right, right.

CW: Yeah, I mean there was also a lot of things going on in the sciences.

LS: Yeah, right.

CW: So when you published the first papers where you could show functional activity in the brain in an animal to the moment that you did it in humans, how much time passed in between.

LS: Well, what had happened was as I said, Ingbar, Lassan and Ingbar had been using something like this with a simulation counters. But they didn't do real functional image, they did functional -- they didn't get a picture of the brain with a function but they superimposed what they thought it was on a brain, so that had been going on in the 60's.

But there's an interesting story about this, by the way. This meeting was held in Varenna, which is a little town on the shore of Lake Como. And I had to fly to Milan, take the train to Varenna, but I remember it was a TWA flight from Washington to New York, and then we had to change from New York to fly to Milan. But it so happened there was something wrong, and the plane, instead of going to, at that time it was called Kennedy Airport, was Idlewild Airport, the plane went to LaGuardia. And they had to take it -- we had to get on -- TWA, it was responsible for this mix-up, so they put a whole bunch of us on a bus and drove us from LaGuardia to Idlewild. So they took all that luggage off of the old plane and they put it on the sidewalk to load the bus. Well when I arrived in Milan one of my suitcases was missing -- actually my suitcase was missing, and in my suitcase was my slides. So I arrived at the meeting on Sunday and I called TWA and TWA said, "Don't worry about it. We'll find it, we'll deliver it in time." And my talk was scheduled at nine o' clock in the morning, on Tuesday morning of this meeting, the meeting that go for a whole week. And I didn't have any slides.

Now this was an organized meeting so there were topics, and my talk was the lead-off talk for that topic on that Tuesday. So I didn't know what to do because if I didn't have my slides I couldn't give my talk, and if I didn't have my slides and couldn't give the talk, I couldn't delay it to later in the week because it would have been out of context, so I didn't know what to do. David Ingbar was at this meeting, the one from Sweden, and the Monday night we were having dinner together, and I had a talk at nine o'clock on Tuesday morning and I said, "I don't know what I'm going to do. I don't have the slides and I really -- I can't. What's the point in postponing it? I would be out of context? I don't really know what to do." And he said to me, "You remember when I visited you a few months ago and you gave me a copy of a manuscript you had written?" I said, "Yes." He said, "Would it help you if you had that copy." I said, "Yeah, that had about 75% of what I'm going to talk about." He said, "Well I have to confess something. I put it in my briefcase and I never took it out, and I have my briefcase here." So he gave me the manuscript and it had figures, tables, these things here. This thing I didn't have unfortunately, but it had these tables and so on. So I went up to the lecture hall that evening where I was supposed to -- where the meeting was to be held, and since I was the first talk in the morning. I put these graphs and these tables on the blackboard. It took me about an hour to put it all on the blackboard, then I started walking out. And as I'm walking out -- I went out and I found somebody, and I asked them, "How do you say, 'do not erase' in Italian?" And I'll never forget it, they said, "Oh, it's prego non cancelado [spelled phonetically]" So I went back and I wrote that on the board, and the next morning I came in, it was all on the board, and I gave what was, I think, a twenty-minute talk. And during the intermission, I don't know if you know the name Ralph Gerard, you ever hear that name? Ralph Gerard at that time was one of the leading neurochemist, neurophysiologist. In fact it was his lab that the microelectrode was invented. He was at the meeting and he said, "You know, that's the best talk I ever heard you give." Anyway.

CW: Now you will never forget about that one, that's for sure.

LS: Yeah, right.

CW: So once you got the matter working, was it difficult to convince the scientific community or funding institutions to accept it, to use it?

LS: Let me get to that part then, yeah. If we have time, there's a very funny incident. So in 1975, we published one in *Science*, but that was just giving images of functional activation; it didn't give any quantitative data, because we hadn't published the method of how to quantify yet. We had reported that in that ten minute talk in '74, but we hadn't written the paper yet. In '76, we used it again non-quantitatively to show the ocular dominance columns in the striate cortex, and the organization of the visual system in the monkey, in the binocular visual system, again with no quantification. At that time one of the fellows in the lab, Sakurada [spelled phonetically] who was from Japan, he was working with us on this method. He had come in 1974 just before we presented it, and it was in 1976, one day he said to me, "Is there something wrong with the deoxyglucose method?" And I said, "No, why do you ask?" He said -- well he had a friend from his same department in Japan who was a research fellow in Dr. Pisano's laboratory, which is the Laboratory of Neurochemistry and Neurology Institute, and he told Sakurada that Dr. Pisano, who is a world-famous neurochemist, had said, "There must be something wrong with the deoxyglucose method because they reported it in 1974 and they never published a paper, so there must be something wrong with it." So then, "A-ha," I said.

At that time I was editor-in-chief of the *Journal of Neurochemistry*, and that kept me almost full-time, I didn't have time to write papers myself, especially one like this, which was a very complicated one, as you can see. A very complicated paper with a lot of mathematics. So I decided to resign as the editor-in-chief of the *Journal*, so I could write this paper, which I did. And sat down in '76, wrote the paper, and in '77 it came out. And that's this paper here if you want to see it. It's an interesting story. And then when the paper came out, we started getting people coming from all over the world as fellows. Actually my first fellow from Germany was somebody named Volker Noiser [spelled phonetically] who was sent by the Bayer Corporation. They had heard about the method so they sent him to learn the method. I don't know what's happened to him since.

And then people came from all over the world so we had an opportunity to start applying the method to all kinds of conditions, all kinds of physiological conditions, pharmacologic conditions, pathological conditions, and finally in 1981…

CW: So was it then, after you published this paper that you started to work with the computer scientists here at the NIH?

LS: Oh, well no, no. It didn't come out that way. NIH didn't have a PET program at the time. What had happened was that from Washington University, Ter-Pogossian, Michael Phelps and Ed Hoffman had built a PET scanner. And we had had several times during the 70's Ter-Pogossian give presentations at meetings about oxygen and blood flow tracers for fifteen [?] labeled water as a blood flow tracer, about images you can get with PET, but there had been no method that would allow you to calculate or measure anything other than pictures. So nobody was interested in, particularly in PET except Ter-Pogossian and his group.

Now in 1977, when the method had been worked out in autoradiography, Marty Ribich who had been in -- he was a neurologist. So he was at the department of neurology at the University of Pennsylvania, and had been collaborating with us on the development of the deoxyglucose method. He came here on a visit and he said, "Well now that we have it working in animals, how about using it in man?" I said, "Sure, if you could find some country in the world where they'll allow you to check deoxyglucose at the [unintelligible] before they decapitate them. We could do it, but I don't think there's any place in the world that's possible. Besides I don't know of a micro tube big enough to cut a human brain". He said, well while he was at Penn, since he was at Penn, he had met David Kuhl, K-U-H-L, who was in nuclear medicine at the University of Pennsylvania, and Kuhl and his associates had developed a single photon scanner that allowed them, by putting four scintillation counters arranged in a square rotating around a head, to be able to record gamma emitting radiation, and get an image for a slice of brain at a time of the concentration of the tracer.

So I said, "Well, yeah. Okay, we wouldn't have to use radiography then. That's possible, however there's a problem. Deoxyglucose has carbon, hydrogen and oxygen in it." Oxygen has a two-minute half-life, carbon-11 has a twenty-minute half-life, and hydrogen doesn't have any gamma-emitting isotopes. And in order to detect the radiation coming out of the brain, you can't use beta emitters, you have to use a gamma emitter, and I don't know how you can synthesize deoxyglucose with a gamma emitter. Carbon-11 and oxygen-15, they don't -- the half-life's too short. However, then I remembered, I belonged to a wine-tasting group of mostly biochemists from the NIH, and in the group was a fellow named Peter Goldman who was biochemical pharmacologist, and his field of work was fluorinated analogs of natural compounds. And he had reported in -- he had written a review in fact in *Science*, I think, in '65. No maybe it was later than that, '75, I don't know. But it was before, and he had pointed out that a fluorine atom is such a small atom. If you put it on a normal, natural molecule in a place that wasn't critical on that molecule, in place of a hydrogen, it didn't interfere always with the action of the enzyme on that molecule. The enzyme wouldn't be able to tell the difference.

So, for example, he had made fluoroglutamate and found that it was converted to fluoro gamma-aminobutyric acid, which is an inhibitory neurotransmitter; the enzyme didn't recognize the difference. So I thought, "Well maybe if we put a fluorine, fluorine-18 as a gamma emitter. If we put it on a not critical part of the molecule, like on the two carbon position, maybe it'll work." But we needed a radio chemist who would know how to do it. So David Kuhl knew Alfred Wolf who was the radiochemist at Brookhaven National Laboratory, and Al Wolf was probably America's leading radio chemist in the country. So a meeting was arranged, we met in Philadelphia. I was there, Ribich was there, Kuhl was there. Alavi, who was the head of nuclear medicine at the University of Pennsylvania, and Wolf and his assistant Joanna Fowler were there and we met and discussed this, and they said -- "Can you make this?" And they said yes, they think could synthesize it. So then I asked, "First of all, I want you to make me carbon-14 labeled fluorodeoxyglucose because we don't know whether it would behave like deoxyglucose if it has the fluorine on it, so first we have to do the experiments with it. And so they made me carbon-14 fluorodeoxyglucose.

CW: So did you start quantifying?

LS: Pardon?

CW: When did you start quantifying? When you did your animal studies or?

LS: That was done with the animal studies, it was all worked out…. Oh here it is. Yeah, this is the paper, the Ribich paper. It was the same method as in animals, but instead of using autoradiography, we used a single photon scanner. But here's the experiments with the fluorodeoxyglucose labeled with carbon-14 in rats to show that it was -- that the enzyme, this is the biochemical studies we did, it showed that the enzyme was -- brain hexokinase was converting fluorodeoxyglucose [unintelligible] just like deoxyglucose, and that if you injected fluorodeoxyglucose into an animal, you got an autoradiographic picture just like you got with deoxyglucose. So now it was okay to go ahead with the fluorine-18, and so you made fluorine-18 and in that paper came the first human images with the fluorodeoxyglucose method. Here we are. Not nearly as good as the autoradiography method, because the autoradiography method gives us 100 micrometers resolution, and this would give us a couple centimeters. And the best PET scanners now, maybe two millimeters, so two millimeters versus a hundred micrometers is quite a difference in resolution.

Well anyway, so this was the publication of the first human application of the fluorodeoxyglucose method. Now at the time, if you notice, oh not this paper, where is it? I just had it, which -- oh here. This was the first one, first human fluorodeoxyglucose method. Now if you notice in the authors, there are two names here, Michael Phelps and Ed Hoffman. They were the two people who had worked with Ter Pogossian in the development of the PET scanner at Washington University, in fact they were graduate students then. And Kuhl had hired them to come work with him, so I had never met them, but when Marty Ribich wrote the first draft of this manuscript and I saw it, I saw those names, I asked him, "Who are these people?" And he said that Kuhl had put their names on; he didn't know either. Well Kuhl later on, shortly after this, got the position of Chief of Nuclear Medicine at the University of California, Los Angeles. And he went out there, and he took Phelps and Hoffman with him. And they got the first commercially produced PET scanner that was produced by -- it was the ECAT2 produced by Ortec Corporation, which was later bought by CTI which is now owned by Siemans [laughs].

And so they went out to UCLA and there they adapted the method for using it with PET scanning because fluorine-18 happens to be a positron emitter, so you can use a PET scanner, a PET scanner gets better images and better resolution than the single photon scanner. So they adapted the method, and that was this paper here.

CW: But before you got in touch with them, and you were still working on animals, you got in touch with the computer people here at the NIH, Wayne Rasband to develop the NIH --

LS: No, no.

CW: That was later?

LS: No, that had nothing to do with PET.

CW: Oh. So, but was it before?

LS: What happened was that was Wayne Rasband and those in that area, it was around 1978 or '79, when we were still working on the autoradiographic method. It was an interesting session. In order to do the quantification, one had to measure on each image, in each structure, the optical density, the darkness of the film. So they had what's called a densitometer. You put the film on the densitometer, and it's a little tiny light which was two millimeters thick that would go through a bright light. And you put the film over so that the light's going through the part of the area of the brain that you're interested in, and then you lower an arm down and press it so light sealed it and you open the shutter and there's a photo multiplier tube [?] that picks up the light. It measures how much light had come through, and from that you can get optical density, and from that, from the calibrated standards, you would get the concentration, which was needed to find the equation. Well it would take hours to do one rat because the many -- you had to take hundreds and hundreds of these readings.

So one time Sakurada and I and Kennedy, Charles Kennedy who had worked with me for all these years, were discussing some of the data. And they had some data, I remember, on the caudate nucleus. And I guess we were preparing to write a paper, and they were putting down all of these individual structures, these are regions that were read. But there are hundreds, thousands of structures in the brain, so it would take hours to do this. And I remember I had asked them about the caudate nucleus, the caudate-putamen, which is a pretty big structure, even in a rat brain. And I asked them, "How many readings did you take?" So they said, well they took three on each side, for each slice. So I said, "That's a big structure. Well, we put a table down and say caudate-putamen, people are going to assume that's the average for the whole caudate-putamen, but how can you tell what the average is from reading three on one side, three on the other?" So Kennedy got angry, he said, "That's easy for you to say, you sit in that chair all day, but we spend hours on this thing, how many more readings do you want us to take?" Well he was right, so we figured, "There must be some way to use computers and automate this. Why can't we put the film in and have it slide through and have a detector?"

So we consulted Wayne Rasband, who was in the what was the Research Services Branch at that time. He was the computer man there, and he helped us design it. Buying parts and putting it together, both from electronics and and helped in scanning the microdensitometer where you put the film in, it rotates and automatically reads every spot at fifty microns all the way through the film, and you needed a computer to store all this huge amount of data. And we got set up. What we did is at first you took a black and white -- black, gray and white film, and we recorded all the optical density, then we could, by the computer, reconstruct the image and put it on a oscilloscope screen in black and white. So what did we gain? I mean, all we got was a big image of what had been a little one. We needed a third dimension, what we needed was to reconstruct the images just they way it had been on the film, but we had to put in a third dimension, which was the rated glucose utilization. Well how do you get a third dimension on a two-dimensional image? Color scale. There's an interesting story about that, too.

So we started making colors so that each rate of glucose utilization would be a certain color. It couldn't be for each individual bias we had to make it as a range, like a color between fifteen and twenty, between twenty and twenty-five be a different color. And we tried, we spent two months trying to figure out what kind of color scale, and this is very interesting. You can arrange arbitrarily the colors for what you want, and we had people come and look and ask which do you like best? And maybe it's something biological, by far the people who liked it the best, the color scale that people liked the best was the spectrum. They liked going, "The low value should be blue, and as you get higher and higher in values it should red and yellow." Except -- I'll tell you this story later, it's special.

So at that point Wayne Rasband said, well he doesn't work for us, he has other things to do, he doesn't have time to do the programming for the color scale. But Charles Goochee was in our laboratory, and he had been working with us on this. So he was in the evening studying at the University of Maryland in chemical engineering, he was going for a degree in that. And he had, of course computer science, so he said, "Do you mind if I try programming this?" I said, "Sure." So he did. Charles Goochee worked out the programming for making the color scale, and actually that was done in '77 because we had had a collaboration with Mort Mishkin in the Laboratory of Neuropsychology, and with a postdoc Charlene Jarvis who later became a D.C. Councilman. And working on monkeys where one side of the brain was being blinded by cutting the optic track, so one of them looking -- using the deoxyglucose method to show which parts of the brain were affected by this. And the first time we color-coded those, and she presented at the Neuroscience Meeting in St. Louis in 1978, and it was a sensation I have to show you this. I'm almost finished. This came out in 1978.

These are the images that Charlene Jarvis presented at this meeting in her talk, and it's a very apt title, "Visualizing Brain Chemistry in Action." And this shows the visual cortex of the monkey in which one side had been blinded by cutting an optic track. And this is the blind hemisphere and the visual cortex is the other one, and you see the change right there. But this produced quite a sensational effect. The way we got involved with -- all right, you have a few minutes?

I said there were people who didn't like that color scale. Well in order to buy the optronics microdensitometer it was very expensive, $60,000 at the time and we didn't have it. So I went to Dr. John Eberhart, who was a scientific director, and I asked him if we could have that extra money, he gave it to us. When we got our first image I thought we should show him what he had gotten for the money he gave us. So I called him and he looked at the picture. So we were disappointed, he wasn't impressed at all. So I remember, I was in his office -- the outer office, I was talking to his secretary, Margaret and I said, "You know, Dr. Eberhart doesn't seemed to be very impressed, but everybody is raving about it." And she said, "Well of course, he's colorblind." So colorblind people didn't really care for that scale.

At any rate, the people at UCLA started using the PET -- this was Kuhl and Phelps and Hoffman and all, collaborating with a neurosurgeon Crandall who was working on epilepsy, neurosurgical treatment of epilepsy. And there was a meeting in Mexico City, the Pan America Neurological Meeting, at which Crandall presented the results with the PET scan before deoxyglucose, in these patients. Don Tower, who was then Director of the Neurological Institute, and Tom Chase, who was then their Scientific Director, they had gone to this meeting and they came back raving, "NIH should have a PET scanner. They should have a PET scanner." And they were the first to bring their PET scanner in, and they started the PET program here. And in the early days I was involved a lot with it but I no longer have anything to contribute. Now it's just applications in areas that I don't know much about. Also I like the resolutions because you really see in the brain individual structures that you recognize, they look just like a histo-stained section. The resolution with PET, even though it's better than it used to be, still you have to do statistical tricks to try to decide which structure you're really looking at, you don't really know.

And I'm a basic scientist, I like to know. Ed Hoffman was at a meeting talking about a new design of a PET scanner which was going to improve resolution. And somebody in the audience said, "What about -- you haven't included in your design time of flight". And his answer was -- well, he didn't think that was important because if you don't know where you are what difference does it make what time it is? So I'd like to know what structure I'm -- not where in the brain I'm looking at, not a chunk of brain, because the nitrous oxide gave me a chunk of brain, the whole brain. I want to know which unit, anatomical unit, of the nervous system that dealing I am working with, because I'm a basic scientist. So I have sort of withdrawn a little bit from PET direct involvement.

CW: That sounds like you're a little bit disappointed about the results that were finally yielded.

LS: No. I think they're doing the best they can, and I think for a lot of things it's very useful, especially nowadays. It's very good for finding tumors. In fact I think it's being used now for that more than for anything else, but it's good for epilepsy, it might be good for early diagnosis of Alzheimer's. But you really want to know about a lot of things, like what we've been doing is using individual pathways and seeing how they function under certain conditions, and under brain development and maturation and we've been doing it in mice now, with genetic knockout, genes knockout, and back to thyroid by the way. Yeah, we're looking at animals with thyroid hormone receptors knocked out, and then seeing what that does to the development of the function in individual structures of the brain, and functional activity, so you can't do that with PET really. But it's good for clinical work, but you know for clinical work you don't need the precision and the exactness.

CW: Anything else you want to put on this?

LS: Well essentially I think we're finished. I can tell you the story, this about Ralph Gerard. Ralph Gerard was a wonderful raconteur. He could tell stories so that at scientific meetings he finally got picked to be the final one at the banquet of the meetings to be a summarizer of what happened at the meeting, and he used to tell wonderful stories. And one of the stories he told was about, at a scientific meeting, at the FACEB meeting, a scientist there had been picked up by a prostitute. And he went to her apartment and when he was getting dressed to leave, he noticed on the wall there was a framed diploma from Vassar College. So he asked her, "Is that yours?" "Yeah, yeah it's mine." As he puts on some work clothes he sees there's another framed diploma, a Masters degree from Columbia University. So he says, "Is that yours, too?" She said, "Yeah, yeah sure." So finally he's putting on his tie, he sees there's another framed diploma. It's a Ph.D. from Harvard. He says, "Is that yours, too?" She says, "Yes." He says, "Well, look. You don't have to answer if you don't want to, but I can't help but being curious. How does somebody with a Bachelors at Vassar, a Masters from Columbia, a Ph.D. from Harvard, how in the world did you ever get into a line of work like this?" And she said, "Oh, I don't mind answering you." "Luck, just luck." She says. So this is -- as you can see there was a lot of steps in here which is luck, just luck or serendipity.

LS: The chairman of the department of physiology and pharmacology where I was a postdoc, Julius Comroe, he was once talking about serendipity, and then he decided maybe some people didn't know what it means. So he said, "I can't tell you -- I can't define it, but I give you an example of what it is. It's like looking for a needle in a haystack and finding a farmer's daughter." So it really was a whole bunch of steps of, really, lucky fortuitous chances, you know?

CW: That's amazing.

LS: So it's been fun.

CW: Yeah, I imagine.

LS: But everything was built one on top of another. It started with, you know, I was lucky and the Surgeon General made me a psychiatrist, I was lucky to come to work with Seymour Kety, I learned a great deal about how to model with someone then going to France and then talking to Don Tower and that's how I guess things are done.

CW: Your early interest in schizophrenia and psychological disorders, are you still interested in that?

LS: Well I would love to know what is the basis of schizophrenia -- the biochemical or whatever basis schizophrenia is, but I don't feel that I have the qualifications to answer that, so I can only be interested in it, but I don't feel I could do anything any better than other people. The same thing happened with development of the method. Once it was developed and we trained a lot of people and a lot of people now don't even have to come here for training; they learn it from others. They use it for areas that they can do much better than I can. I'm not a neuropsychologist, so why should I do neuropsychology? I should do what I do best.

CW: Yeah, sure. Did you talk to Robert Cohen?

LS: Yeah Robert Cohen was in this lab too. He was the head of the Mental Health Institute PET program originally. Originally it was an old NIH program, but then it got separated and each institute had its own separate programs, and they used the PET program like a gas station. You go up and fill up the tank, they run everything, but they don't do much of their own research anymore, and that's not interesting.

CW: So when did you stop working here officially?

LS: Well technically I retired in July.

CW: In July?

LS: Yeah, but we haven't moved out of here. When we move out of here I will stop, except writing. But for the time being I'm still able, because there's still a laboratory here, to continue doing some work, actually in collaboration with some of the PET people. They developed a small animal PET scanner, so we're helping them show what it can do by comparing side by side whether you see with the same animal, with the PET, and what you see with radiography. But when we move out of here I won't have a lab.

CW: So this will be a big change.

LS: It'll be a big change, yeah. But I still have such a background of things to write up, I have so many things to write, because you can get data faster than you can write it up, at least for me.

CW: So this premise that PET would have understanding of normal and abnormal brain physiology and drug delivery in the brain and all that, that does not seem to have become really true about it.

LS: Well, you know measuring glucose utilization isn't going to answer the question of what's wrong; in fact that's what I used to say many times. The deoxyglucose method is not going to tell you what in the brain is wrong it can only tell you where to look by other methods. It's sort of like what the -- Dave Hubel of the Hubel and Wiesel you know the names? I once said that the deoxyglucose method was like putting a thousand electrodes into the brain at once because before they were always recording by one electrode at a time.

CW: Thank you very much.

CW: So you were interested first in function when you knew you were interested in blood flow, but then you quickly said that it's not the blood flow in the entire brain, but it's blood flow in specific regions that you want to look at.

LS: And then metabolism.

LS: But then it was to localize where the function was, normal or abnormal. But it can't tell you what is wrong with the function, it can only tell you where it's wrong. Other methods are needed to, yeah.

CW: And this relationship between function and blood flow or glucose levels, did that work out the way you thought it would?

LS: That we've always been interested in, two areas where we've done a lot of work. Again, as I said, we do basic work, what are the mechanisms, which is what basic scientists want, they would say "mechanism," why does functional activity increase glucose metabolism? What is there about functional activity? And there we show that we did a lot of work there, where functional activity in the nervous system is spike activity. You know, they fire and they conduct. Well, what's a spike? Spike is the result of sodium moving into the cell and potassium coming out. Well, how does that increase metabolism? Well we did show that the increase in metabolism is directly related to the spike frequency. If you stimulate a pathway, you find that at the terminal zones of the pathway, that if you increase the frequency, the stimulation frequency, you increase the metabolism linearly, straight.

CW: So would you say that the ability to produce these colored pictures of the brain, was it more successfully in terms of convincing others of what you did than for your own understanding of what was going on?

LS: Yeah.

LS: It just made it easier and more visual for people. But you didn't necessarily see it any more than you could see from the autoradiographs. It was a way to present it better. It's sort of like black and white television versus colored television, you know? But we did a lot of work, which I haven't even mentioned here about the mechanism. Why does functional activity stimulate glucose utilization, and we answered that question. It's due to the fact that when sodium comes in and potassium comes out, the membrane potential will decrease and you have to restore the membrane potential, which means you've got to pump the sodium out and pull the potassium in. And that's with ATP. So you have to regenerate the ATP. To regenerate the ATP, you have to put in energy, where's the energy coming from? Glucose utilization, so that we showed, those are the basic research that we were doing, not disease-oriented. I leave the disease for the doctors. I study processes.